

**REMARKS/ARGUMENTS**

With this amendment, claims 53, 55-57, 61, 66-68 and 73-74 are pending. Claims 1-52, 54, 58-60, 62-65, and 69-72 are cancelled without prejudice to subsequent revival. For convenience, the Examiner's rejections are addressed in the order presented in a June 12, 2007, Office Action.

**I. Status of the claims**

Claim 53 is amended to recite a method for producing sialyllactose by expressing a heterologous  $\alpha$ 2,3-sialyltransferase protein and a heterologous CMP-sialic acid synthetase protein in an *E. coli* cell and contacting the cell with lactose to allow formation of the sialyllactose. Support for this amendment is found throughout the specification, for example, at original claim 71. Production of sialyllactose is exemplified at pages 59-61. Amended claim 53 also recites the activities of the a heterologous  $\alpha$ 2,3-sialyltransferase protein and a heterologous CMP-sialic acid synthetase protein. Support for these amendments is found throughout the specification, for example, at page 20, lines 20-25 and page 34, lines 18-26. These amendments add no new matter.

**II. Rejections under 35 U.S.C. §112, first paragraph, written description**

Claims 53, 55-58, 60-70, and 72-74 are rejected under 35 U.S.C. §112, first paragraph for allegedly failing to comply with the written description requirement. According to the Office Action, the specification lacks description of the claimed invention, such that a skilled artisan would recognize that Applicants had possession of the claimed invention at the time of filing. To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection. Claim 71 was not rejected for lack of written description. Applicants have amended claim 53 to include the limitations of claim 71 and believe that this amendment overcomes the rejection for alleged lack of written description. All other pending claim depend from claim 53, and thus, also include the limitations of claim 71. In view of these amendments

and remarks, withdrawal of the rejection for alleged lack of written description is respectfully requested.

### **III. Rejections under 35 U.S.C. §103(a)**

The Office Action maintains rejections for alleged obviousness in view of various combinations of references. To the extent the rejection apply to the amended claims, Applicants respectfully traverse the rejections.

The Office Action has not established a case of *prima facie* obviousness. To establish a case of *prima facie* obviousness, the Examiner must meet three basic criteria:

First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). M.P.E.P. §§ 706.02(j) and 2143.

The references cited by the Examiner fail to provide a reasonable expectation of success in practicing the invention and fail to provide a motivation for the combination of the references. In addition, the references cited by the Examiner fail to provide all the elements of the rejected claims. Therefore, Applicants respectfully traverse the rejections.

#### *A. Samain et al., Ullrich et al., and Fujio et al.*

Claims 53, 56-58, 60, 65-70, and 72-74 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Samain *et al.*, *Carbohydr. Res.* 302:35-42 (1997); in view of Ullrich *et al.*, *J. Bacteriol.* 177:6902-6909 (1995); and Fujio *et al.*, *Biosci. Biotechnol. Biochem.* 61:840-845 (1997). Claim 71 was not rejected in view of this combination of references. Claim 53 and its dependent claims are now amended to include the limitations of claim 71. In view of this amendment, withdrawal of this rejection is respectfully requested.

*B. Samain et al., Ullrich et al., Fujio et al., and Bulow et al.*

Claims 61-65 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Samain *et al.*, in view of Ullrich *et al.*, Fujio *et al.*, and Bulow *et al.*, *Trends Biotech.* 9:226-231 (1991). The amended claims are directed to a cell based method of producing sialyllactose. The host *E. coli* cells comprise a heterologous  $\alpha$ 2,3-sialyltransferase protein and a heterologous CMP-sialic acid synthetase protein. None of the cited references provide any motivation for production of this oligosaccharide using this combination of heterologous enzymes. Moreover, Samain *et al.* actively teach away from the use of a heterologous accessory enzyme, such as a CMP-sialic acid synthetase protein. In fact, Samain *et al.* teach away from use of anything other than the endogenous *E. coli* sugar nucleotide pools maintained by endogenous enzymes, stating at page 36, left column that UDP-GlcNAc is maintained at "quite high" intracellular levels in most bacteria, thereby providing ample substrate for the NodC protein. Samain *et al.* also cautions that over expression of recombinant gene products can be unfavorable to oligosaccharide synthesis by causing "unnecessary metabolic burning, a growth inhibition by overproduced proteins, and problems of precipitation and misfolding of proteins." Samain *et al.* page 39, left column. Samain *et al.* warns those of skill against over expression of proteins generally, including over expression of multiple proteins and thus, does not provide a reasonable expectation of success or a motivation to combine expression of a heterologous  $\alpha$ 2,3-sialyltransferase protein and a heterologous CMP-sialic acid synthetase protein, or other pairs or glycosyltransferases and accessory enzymes, as suggested by the Office Action. In view of Samain *et al.*'s warning against protein overexpression, this combination of references does not render the claimed invention obvious.

*C. Samain et al., Ullrich et al., Fujio et al., and Tullius et al.*

Claim 71 is rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Samain *et al.*, in view of Ullrich *et al.*, Fujio *et al.*, and Tullius *et al.*, *J. Biol. Chem.* 271:15373-15380 (1996). The Office action alleges that Tullius *et al.* discloses the cloning and expression of a CMP-sialic acid synthetase from *Haemophilus* and that this disclosure provides motivation for those of skill to practice the claimed methods. As above, Samain *et al.* warns against

overexpression of recombinant proteins. Tullius *et al.* at page 15377, left column, discloses that overexpression of the CMP-sialic acid synthetase from *Haemophilus* in *E. coli* is, in fact, toxic to the *E. coli* cells. Most of the CMP-sialic acid synthetase recovered from the *E. coli* cells was found in an insoluble fraction of the cell. The combination of the warning of Samain *et al.* and the toxicity described in Tullius *et al.* does not provide a reasonable expectation of success. Thus, the citation of Samain *et al.*, in view of Ullrich *et al.*, Fujio *et al.*, and Tullius *et al.* fails to render the claimed methods obvious.

In view of the above amendments and remarks, withdrawal of the rejection for alleged obviousness is respectfully requested.

**CONCLUSION**

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,  
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